POTENTIAL METABOLITES OF THE NEUROLEPTIC AGENT CHLORPROTHIXENE; SYNTHESIS AND PHARMACOLOGY OF THE 3-, 4-, 6- AND 7-HYDROXY AND METHOXY DERIVATIVES OF 2-CHLORO-9-(3-DIMETHYLAMINOPROPYLIDENE)-THIOXANTHENES*

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Cyclization of the acids *IV*—*VII* with sulfuric or polyphosphoric acid resulted in the thioxanthones *VIIIa*—*d* which were treated with 3-dimethylaminopropylmagnesium chloride and gave the amino alcohols *Xa*—*d*. Their acid catalyzed dehydrations afforded the methoxy derivatives of chlorprothixene *IIIa*—*d*, mostly in form of mixtures of geometric isomers. Whereas the results of attempts to demethylate these products with boron tribromide gave mostly unsatisfactory results, the demethylation with pyridine hydrochloride at 190—200°C was successful; alcohols *X* were the most suitable starting materials. In this manner, the hydroxy derivatives of chloroprothixene *IIa*—*d* were obtained, mostly as pure geometric isomers. The configuration was assigned on the basis of their IR spectra. *Z*-Isomers are potential metabolites of the neuroleptic agent chlorprothixene (*I*). Compounds *II* and *III* are little toxic, have low central depressant activity and are inactive cataleptically.

The neuroleptic agent chlorprothixene, 2-chloro-9-(3-dimethylaminopropylidene)-thioxanthene (*I*), synthesized for the first time by Petersen[1,2], was later identified by means of X-ray diffractometry as the *Z*-isomer[3]. In connection with our own experimental work[4], Svátek[5] elaborated a method for differentiating chlorprothixene (*I*) and its *E*-isomer which was successfully used for characterization of geometric isomers of chlorprothixene analogues[6-8]. The method consists in evaluating differences in the region 870–900 cm^{-1} in the IR spectra of the isomers. In spite of the fact that chlorprothixene attained extensive clinical use as a relatively mild antipsychotic agent[9-11], the knowledge of its biotransformation in experimental animals and men has been very limited until present[12,13]. In the first three studies in this line[14-16], the metabolites were isolated from the urine of rats, dogs and patients and successively identified as chlorprothixene S-oxide[14], demethylchlorprothixene S-oxide[15] and chlorprothixene N,S-dioxide[16]. Demethylchlorprothixene was found in the isolated

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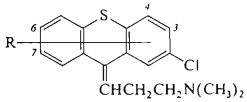
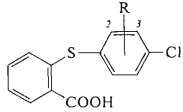
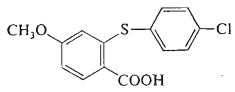
perfused rat liver together with a further metabolite claimed tentatively to be bisdemethylchlorprothixene[17], An analytical study with human blood, liver and urine from fatal poisoning did not enhance the number of the identified metabolites[18]. In a single paper[15] we meet with mentioning the search after phenolic metabolites; whereas they could not be proven in the rat urine, a glucuronide fraction was isolated from the dog urine and its hydrolysis and chromatography gave two products characterized as phenols. Their identification could not be undertaken since authentic samples of hydroxylated chlorprothixenes were not available. With regard to the fact that hydroxylation in aromatic nuclei is a general metabolic mechanism, recognized in a large extent in the case of chlorpromazine[19], we were persuaded that it must



a, 3-R
b, 4-R
c, 6-R
d, 7-R

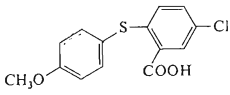
I, R = H
II, R = OH
III, R = OCH_3



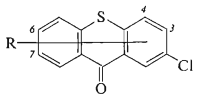


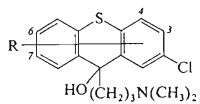
IV, R = 3-OCH_3
V, R = 2-OCH_3

VI



VII





VIII, R = OCH_3
IX, R = H

X, R = OCH_3

play an important role likewise in the case of chlorprothixene and therefore have carried out several years ago the synthesis of several hydroxylated chlorprothixene derivatives as potential metabolites and standards for further metabolic studies; this synthetic investigation is now being described. The publication was prompted by a recent preliminary announcement by Breyer-Pfaff and coworkers[20] of an extensive metabolic study of chlorprothixene in man and dog, in which the hydroxylation of chlorprothixene in all positions of the thioxanthene skeleton, with the exception of position 1, has been suggested.

We carried out the synthesis of chlorprothixene derivatives hydroxylated in positions 3, 4, 6 and 7, *i.e.* the title compounds *IIa–d*, processing *via* methyl ethers *IIIa–d*. Starting compounds were *IV* (ref.[21]), *V* (ref.[22]), *VI* (ref.[23]) and *VII* (ref.[24]). Cyclizations of the acids *IV–VII* gave thioxanthones *VIIIa–d* which were transformed by treatment with 3-dimethylaminopropylmagnesium chloride to the aminoalcohols *Xa–d*. Acid catalyzed dehydrations resulted in the olefinic amines *IIIa–d* which were demethylated. It was also possible to demethylate directly the alcohols *Xa–d*; dehydration proceeded simultaneously. Both routes led thus to the phenolic amines *IIa–d*. Since the methods used in the individual cases were different and the results obtained likewise differed, the course of the preparation of the individual hydroxy derivatives of chlorprothixene (*IIa–d*) will now be described.

In the synthesis of the 3-hydroxy derivative of chlorprothixene (*IIa*), the acid *IV* was cyclized with sulfuric acid at 40°C. Under these conditions, the conversion to the desired thioxanthone *VIIIa* proceeds with a satisfactory yield and the sulfonation is not apparent. The IR spectrum of the product shows a band at 837 cm^{-1} which is explained by the presence of some isomeric ketone *XI*. Reaction with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran afforded the amino alcohol *Xa* which was dehydrated by heating with dilute sulfuric acid. The obtained olefinic amine *IIIa* was isolated as sulfate and represents a mixture of geometric isomers. The amino alcohohol *Xa* was demethylated by heating with pyridine hydrochloride to 190°C. The phenolic base *IIa* was obtained in the form of a solvate with acetone. Since some of the signals in the ^{1}H-NMR spectrum are doubled the substance is a mixture of geometric isomers; the IR spectrum indicates strong prevalence of the *E*-isomer (satelite band at 779 cm^{-1} and a medium strong band at 882 cm^{-1} corresponding to the solitary C—H in position 1 of the skeleton being not in interaction with the side chain; *cf.*[5]).

An attempt to cyclize the acid *V* with sulfuric acid at 90–95°C led to an impure product in a low yield. Polyphosphoric acid was therefore used and the cyclization carried out at 130–135°C; thioxanthone *VIIIb* was obtained in a high yield. The transformation to the amino alcohol *Xb* was carried out like in the preceding case. Similar dehydration gave the olefinic base *IIIb*, isolated as sulfate and considered to be a mixture of geometric isomers. Demethylation with boron tribromide in di-

chloromethane at room temperature and the following alkaline hydrolysis of the primary product resulted in an amphoteric substance, characterized analytically and with spectra as monohydrate of the base *IIb*; the ^{1}H-NMR spectrum indicates again its inhomogeneity (mixture of geometric isomers). It was more advantageous to demethylate the amino alcohol *Xb* by heating with pyridine hydrochloride; the dehydration proceeded simultaneously. The crude product was separated by crystallization into two isomeric bases, the homogeneity of which was confirmed by the ^{1}H-NMR spectra. *E*-Configuration was assigned by means of the IR spectrum to the prevailing and higher melting isomer (presence of the satellite bands at 767 and 787 cm^{-1} and the band of the solitary C—H in position 1 at 849 cm^{-1}). The minor isomer has consequently the *Z*-configuration (absence of the satellite bands in the region 765–800 cm^{-1} and the band of the solitary C—H in position 1 at 874 cm^{-1} influenced by the interaction with the side chain, *i.e.* shifted to higher frequencies). Configurations derived from the spectra are in agreement with conclusions made on the basis of pharmacological activity (Table I).

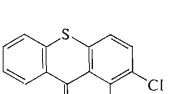
In the series *c* leading to 6-hydroxychlorprothixene (*IIc*), the acid *VI* was first cyclized with sulfuric acid at 95–100°C. Ketone *VIIIc* was obtained in the yield of 60%. As a by-product, a further thioxanthone was isolated which is sulfonated

TABLE I

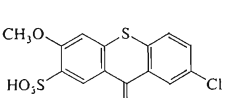
Pharmacological Properties of Chlorprothixenes (*Z-I* and *E-I*) and Their Derivatives (doses in mg/kg)

Compound	Code Number	Administration	Acute Toxicity LD_{50}	Ataxia Rotarod ED_{50}	Catalepsy ED_{50}
Z-I	—	*p.o.*	217	5·2	23
Z-I	—	*i.v.*	38	0·11	2·6
E-I	—	*i.v.*	30	0·83	—
E-IIa	VÚFB-13.723	*p.o.*	2 500	>300	>300
Z-IIIb	VÚFB-13.725	*p.o.*	250	> 20	50
E-IIb	VÚFB-13.724	*p.o.*	2 000	>300	>300
Z-IIc	VÚFB-12.364	*p.o.*	500	> 50	> 50
E-IId	VÚFB-12.365	*p.o.*	>500	55	> 50
IIIa	VÚFB-10.665	*p.o.*	320	115	> 50
IIIb	VÚFB-10.676	*p.o.*	440	128	> 50
IIIc	VÚFB-10.675	*p.o.*	400	110	> 50
IIId	VÚFB-10.671	*p.o.*	350	80	> 50
XV	VÚFB-12.392	*i.v.*	60	> 12	—

in the nucleus; the structure *XII* is tentatively assigned. This structure (*a*) takes into account the reactivity of the respective position determined by activation by substituents and at the same time the relative steric accessibility, (*b*) considers the possibility that the sulfonation could take place before the cyclization; in this case it would not deactivate the nucleus functioning as acceptor of the attack of the acylium cation and (*c*) is in agreement with the spectra. The cyclization of acid *VI* with polyphosphoric acid proceeds again without complications and the ketone *VIIIc* is obtained in a yield of 90%. The conversion to the alcohol *Xc* and its dehydration were carried out similarly like in the series *a*. A homogeneous olefinic base *IIIc* was obtained in a yield of 40% corresponding according to the IR spectrum to the *E*-configuration (with respect to positions of the atom of chlorine and the side chain). The ^{1}H-NMR spectrum confirms the homogeneity of the product without indicating the configuration. In an attempt to demethylate compound *IIIc* with a small excess of boron tribromide in chloroform, a product was obtained which was identified as the aminoalcohol *Xc*; demethylation did not take place. The boron tribromide was probably added to the double bond and the product hydrolyzed resulting in compound *Xc*. In the following experiment, a greater excess of boron tribromide (in dichloromethane) was used and demethylation took place leading to a hydrate of the phenolic base *IIc* for which the IR spectrum indicates the *Z*-configuration. Demethylation of compound *IIIc* was carried out also by heating with pyridine hydrochloride. The product was again the phenolic base *IIc* (not solvated) for which the IR spectrum indicates *Z*-configuration (band of the solitary C—H in position 1 at 908 cm^{-1}, *i.e.* shifted to higher frequency). The same product was obtained by demethylation and simultaneous dehydration of the aminoalcohol *Xc* by heating with a solution of hydrogen bromide in acetic acid. The apparent discrepancy consisting in the fact that the *E*-isomer of compound *IIIc* affords by demethylation procedures the *Z*-isomer of compound *IIc* must be explained by protonation and transitional formation of carbonium cation (very likely especially under the hard conditions of the demethylation with pyridine hydrochloride) enabling in the folfollowing stage the formation of a product with inverse configuration on the double bond.



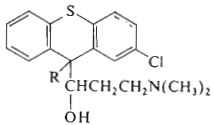
XI



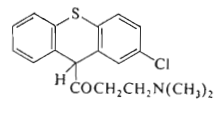
XII

In the series *d*, leading to 7-hydroxychloroprothixene (*IId*), the acid *VII* was cyclized with sulfuric acid at 20°C; thioxanthone *VIIId* was obtained in a yield of only 35%. It was transformed in the usual way to the amino alcohol *Xd* which was de-

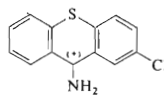
hydrated by boiling with dilute sulfuric acid. The olefinic base *IIId*, obtained in the form of crystalline salt, was characterized by the ^{1}H-NMR spectrum as a mixture of geometric isomers. Demethylation was carried out with the amino alcohol *Xd* by treatment with pyridine hydrochloride. The phenolic base *IId* obtained is homogeneous (^{1}H-NMR spectrum) and the IR spectrum showed the *E*-configuration. The diagnostic tool in this case was the band at 3300 cm^{-1}, not disappearing even at high dilution, attributed to the phenolic hydroxyl in hydrogen bond with the nitrogen atom of the side chain; the same band was observed with the *Z*-isomer of the 2-hydroxy derivative of prothixene[7]. The same product was obtained from the alcohol *Xd* by dehydration by boiling with a solution of hydrogen chloride in acetic acid and by the following heating with pyridine hydrochloride.



XIII, R = Br
XIV, R = NH_2



XV



XVI

Körbl and Jančík[25] observed during the bromometric estimation of *Z*-chlorprothixene (*I*) with bromate–bromide reagent in a mixture of acetic and hydrochloric acid and after the following treatment with alkali the formation of a solid product to which the structure of the "corresponding" bromohydrine was assigned, *i.e.* of the product of hypobromous acid addition. Now, this reaction has been investigated as a preparative one and the product was subjected to thermic decomposition. Because of an extreme reactivity of the bromine atom, the structure *XIII* was assigned to the primarily formed bromohydrine with the atom of bromine on the benzhydryl α-carbon. Thermic decomposition was carried out by heating to 130°C. Crystallization gave the main product which was formed by dehydrobromination of the bromohydrine *XIII* and identified as the amino keton *XV* (spectra). Chromatography of the mother liquor gave very small quantities of 2-chlorothioxanthone (*IX*) (ref.[4]) and *Z*-chlorprothixene (*I*) (ref.[1,4]) which were first eluted from the column; the ketone *IX* is apparently a product of oxidation of chlorprothixene (*I*). The most polar component of the mixture was a diamine, giving a dihydrochloride, corres-

ponding according to the analysis to the elemental composition $C_{18}H_{23}Cl_3N_2OS$. The mass spectrum did not find the molecular ion of the base having the expected composition $C_{18}H_{21}ClN_2OS$. The two main fragments $C_{13}H_9ClNS$ (*XVI*) and $C_5H_{12}NO$, the sum of which is just the expected empirical formula of the diamine, determine the structure of this compound to be *XIV*. This diamine was evidently formed by a nucleophilic substitution of the bromine atom in the molecule of the bromohydrine *XIII* with ammonia used for making the mixture alkaline. The unequivocally shown structure of this diamine represents at the same time a further argument for the structure *XIII*, assigned to the bromohydrine.

All of the prepared hydroxy and methoxy derivatives of chlorprothixene (*IIa–d*, *IIIa–d*) and the amino ketone *XV* were pharmacologically evaluated on the one hand as potential neuroleptics (incoordinating and cataleptic activity), and quite generally by methods of the pharmacological screening on the other (Dr M. Bartošová, affiliated unit of this Institute at Rosice n/L). The salts, described in the Experimental, were used for the evaluation; the doses given were calculated for bases. Results of the psychopharmacological screening are summarized in Table I, including also Z- and *E*-chlorprothixene (*I*) (*ref.*[26,27]). The table shows the medium lethal doses for mice LD_{50} on oral or intravenous administration, the medium effective doses (ED_{50}) bringing about ataxia in the rotarod test in mice, and finally results obtained in the test for cataleptic action in rats where only for Z-chlorprothixene (*I*) and its 4-hydroxy derivative *IIb* the medium effective doses ED_{50} could be estimated. As apparent, all the chlorprothixene derivatives, having oxygen functions, are little toxic, have a low incoordinating activity and with the exception of compound *IIb* are cataleptically inactive. Compound *IIId* was also evaluated for the influence on the locomotor activity of mice by the photo-cell method (medium effective dose ED_{50} = 16·3 mg/kg *p.o.*) and for the antiapomorphine activity in rats (an oral dose of 40 mg/kg does not influence the apomorphine chewing and reduces the apomorphine agitation to 89% in comparison with 100% in the control group). Both results indicate some central depressant activity of the substance while the neuroleptic effect was absent.

Compounds *E—IIa*, *E—IIb* and *XV* were evaluated by a battery of tests using methods of the general screening. Basic doses (D) used in the tests *in vivo* and the effective doses (ED) for the individual types of activity (all the doses in mg/kg) are given. *E—IIa*: D = 300 *p.o.*; antihistamine activity (dose protecting 50% guinea-pigs from the lethal effect of 5 mg/kg histamine administered intrajugularly), ED = 100—300 *p.o.* (for embramine as a standard, ED = 1—2·5 *p.o.*); CNS effect (dose inhibiting significantly the motility of mice in known surroundings), ED = 300 *p.o.* *E-IIb* : D = 300 *p.o.*; antihistamine activity, ED = 300 *p.o.* *XV*: D = 12 *i.v.*; local anaesthetic effect (concentration bringing about a complete anaesthesia in 50% guinea-pigs in the test of infiltration anaesthesia), ED = 0·1—0·5% (for procaine as a standard, ED = 1%); spasmolytic (parasympatholytic) effect (concentration exhibiting a reduction of the acetylcholine contractions of the isolated rat duodenum by 50%), ED = 0·1—1 μg/ml (for atropine as a standard, ED = = 0·05 μg/ml); spasmolytic (musculotropic) effect (concentration exhibiting a reduction of barium chloride contractions of the isolated rat duodenum by 50%), ED = 1—10 μg/ml (for papaverine

as a standard, ED = 5 μg/ml); influence on diuresis in mice, the dose D *i.v.* decreases strongly the diuresis; thiopental potentiation (dose prolonging the duration of the thiopental sleeping time in mice to 200% of the control value), ED = 5—12 *i.v.* (for chlorpromazine as a standard, ED = 0·5 *i.v.*); negative inotropic effect (concentration eliciting a decrease of inotropy of the isolated rabbit heart atrium by 25%), ED = 25—50 μg/ml.

Some of the compounds were also tested for antimicrobial activity *in vitro* (Dr L. Langšádl and Dr J. Turinová, bacteriological department of this Institute). The used microorganisms, numbers of compounds and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus* β-*haemolyticus*, *IIIb* 50, *IIIc* 50, *IIId* 100; *Streptococcus faecalis*, *IIIa* 50, *IIIb* 50, *IIIc* 50, *IIId* 25, *XV* 100; *Staphylococcus pyogenes aureus*, *IIIb* 50, *IIIc* 25, *IIId* 25, *XV* 12·5; *Mycobacterium tuberculosis* H37Rv, *E-IIa* 50, *E-IIb* 12·5, *IIIa* < 5, *IIIb* < 5, *IIIc* < 5, *IIId* < 5, *XV* 50; *Saccharomyces pasterianus*, *IIIa* 100, *IIIb* 100, *IIIc* 25, *IIId* 50, *XV* 3·1; *Trichophyton mentagrophytes*, *E-IIa* 50, *IIIa* 50, *IIIb* 100, *IIIc* 100, *IIId* 50, *XV* 1·5; *Candida albicans*, *IIIa* 100, *IIIb* 100, *IIIc* 100, *IIId* 100, *XV* 50; *Aspergillus niger*, *IIIa* 100, *IIIb* 100, *IIIc* 100, *IIId* 100.

EXPERIMENTAL

The melting points of analytical preparations were determined partly in Kofler's block and are not corrected, partly in an automatic Mettler FP-5 melting point recorder. The samples were dried at about 50 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (mostly in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in KBr) with a Unicam SP 200G spectrophotometer, the ^{1}H-NMR spectra (mostly in $CDCl_3$) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectrum with a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by chromatography on thin layers of alumina or silica gel (Silufol). For column chromatography, neutral Al_2O_3 (activity II) was used.

2-Chloro-3-methoxythioxanthone (*VIIIa*)

A mixture of 39·2 g 2-(4-chloro-3-methoxyphenylthio)benzoic acid (*IV*) (ref.[21]) and 225 ml H_2SO_4 was stirred for 2 h at 40°C. It was then poured into a mixture of 900 g ice and 900 ml water, the solid was filtered, suspended into a solution of 10% NaOH and stirred for 10 min at 50°C, filtered again, washed with water, dried *in vacuo* and crystallized from 4·5 l benzene; 30·9 g (84%), m.p. 233—234°C (Mettler). Analytical sample had the same melting point. UV spectrum: λ_{max} 269 nm (log ε 4·67), 257 nm (4·66), infl. 309 nm (3·66), 361 nm (3·79). IR spectrum: 737, 837, 911 (Ar—H), 1 033, 1 242, 1 253, 1 287 ($ArOCH_3$), 1 556, 1 580, 1 587 (Ar), 1 620 cm^{-1} (ArCOAr). For $C_{14}H_9ClO_2S$ (276·7) calculated: 60·76% C, 3·28% H; found: 60·98% C, 3·17% H.

2-Chloro-4-methoxythioxanthone (*VIIIb*)

A mixture of 70 g 2-(4-chloro-2-methoxyphenylthio)benzoic acid (*V*) (ref.[22]) and 600 g poly phosphoric acid was stirred for 3 h at 135°C. It was decomposed with 3 l water, allowed to stand overnight, filtered, the solid suspended in 1·2 l 5% NaOH at 100°C, cooled, filtered, washed with water and dried. The crude product was crystallized from 950 ml xylene; 50 g (76%), m.p. 205 to 206°C. Analytical sample, m.p. 209—210°C (xylene) (Mettler). UV spectrum: λ_{max} 260 nm (log ε 4·65), 300 nm (3·83), 311 nm (4·00), infl. 378 nm (3·73), 391 nm (3·80). IR spectrum (Nujol): 744, 865, 894 (4 adjacent and solitary Ar—H), 1 262, 1 350 ($ArOCH_3$), 1 566, 1 583 (Ar), 1 630 cm^{-1} (ArCOAr). For $C_{14}H_9ClO_2S$ (276·7) calculated: 60·76% C, 3·28% H, 12·81% Cl, 11·59% S; found: 60·44% C, 3·44% H, 12·66% Cl, 11·69% S.

2-Chloro-6-methoxythioxanthone (*VIIIc*)

A) A mixture of 26·0 g 2-(4-chlorophenylthio)-4-methoxybenzoic acid (*VI*) (ref.[23]) and 175 ml H_2SO_4 was stirred for 1 h at 95—100°C, cooled and decomposed by pouring into 3 kg mixture of ice and water. The solid was filtered, suspended into 1 l 5% NaOH and stirred for 1 h at 50—60°C, the suspension was cooled and filtered. The solid was dried at 100°C, pulverized and extracted with 700 ml boiling xylene, used in 3 parts. The hot solution was separated from the undissolved substance and allowed to crystallize; 14·6 g (60%), m.p. 211—212°C (Mettler). Analytical sample had the same melting point. UV spectrum: λ_{max} 256·5 nm (log ε 4·55), 270 nm (4·55), 277·5 nm (4·58), 316 nm (3·82), 362 nm (3·74). IR spectrum (Nujol): 809, 837, 879, 903 (2 adjacent and solitary Ar—H), 1 240, 1 252 ($ArOCH_3$), 1 487, 1 595 (Ar), 1 630 (ArCOAr) cm^{-1}. For $C_{14}H_9ClO_2S$ (276·7) calculated: 60·76% C, 3·28% H, 12·81% Cl, 11·59% S; found: 60·96% C, 3·13% H, 12·81% Cl, 11·67% S.

The solid insoluble in xylene (12·9 g) was dissolved in water, the solution filtered and acidified with hydrochloric acid. The crystalline product was filtered, washed with 3M-HCl and dried; m.p. 248—252°C (Mettler). Experimental data are compatible with its formulation as 7-chloro--3-methoxythioxanthone-2-sulfonic acid (*XII*) monohydrate. IR spectrum: 827, 849 (2 adjacent and solitary Ar—H), 1 155 (SO_3H), 1 270 ($ArOCH_3$), 1 585 (Ar), 1 632 (ArCOAr), 3 400 cm^{-1} (H_2O). For $C_{14}H_9ClO_5S_2 + H_2O$ (374·8) calculated: 44·86% C, 2·96% H, 9·46% Cl; found: 44·41% C, 3·13% H, 9·59% Cl.

B) A mixture of 30·0 g *VI* (ref.[23]) was stirred with 240 g polyphosphoric acid at 125—135°C for 3 h and processed similarly like in the preparation of *VIIIb*; 25·3 g (90%), m.p. 211—212°C.

2-Chloro-7-methoxythioxanthone (*VIIId*)

A mixture of 22·7 g 5-chloro-2-(4-methoxyphenylthio)benzoic acid (*VII*) (ref.[24]) and 110 ml H_2SO_4 was stirred for 4·5 h at 20°C. It was then decomposed by pouring into 0·75 kg mixture of ice and water and the product was extracted with chloroform. The extract was washed with 2·5M-NaOH and water, dried with K_2CO_3 and evaporated; 7·5 g (35%), m.p. 182—187°C. Analytical sample, m.p. 188—189°C (ethanol–toluene) (Kofler). UV spectrum: λ_{max} 250·5 nm (log ε 4·58), 272 nm (4·44), 282 nm (4·43), infl. 301 nm (3·54), 378 nm (3·81). IR spectrum: 776, 805, 866, 903 (2 adjacent and solitary Ar—H), 1 275, 1 344 ($ArOCH_3$), 1 580, 1 597 (Ar), 1 624 cm^{-1} (ArCOAr). For $C_{14}H_9ClO_2S$ (276·7) calculated: 60·76% C, 3·24% H, 12·81% Cl, 11·59% S; found: 60·78% C, 3·27% H, 12·87% Cl, 11·60% S.

2-Chloro-3-methoxy-9-(3-dimethylaminopropyl)thioxanthene-9-ol (*Xa*)

Grignard reagent was prepared from 5·4 g Mg and 27·2 g 3-dimethylaminopropyl chloride in 70 ml tetrahydrofuran with small amounts of iodine and 1,2-dibromoethane, used for starting the reaction. A suspension of 31 g *VIIIa* in 150 ml tetrahydrofuran was added over 15 min to the cooled Grignard reagent, the mixture was stirred for 1 h at room temperature and allowed to stand overnight. It was then decomposed by pouring into 120 ml 20% solution of NH_4Cl and the product was extracted with chloroform. The extract was dried and evaporated and the residue was crystallized from ethanol; 31·5 g (77%), m.p. 177—179°C. Analytical sample, m.p. 179—181°C (ethanol) (Kofler). IR spectrum (Nujol): 740, 758, 843, 860 (4 adjacent and solitary Ar—H), 1 043 (C—OH in the cycle), 1 259, 1 267 ($ArOCH_3$), 1 483, 1 582 (Ar), 2 600 cm^{-1} (OH···N). ^{1}H-NMR spectrum: δ 7·80 (m, 1 H, 5-H), 7·80 (s, 1 H, 1-H), 7·10—7·40 (m, 3 H, 6,7,8-H_3), 6·89 (s, 1 H, 4-H), 3·80 (s, 3 H, OCH_3), 2·38 (s, 6 H, CH_3NCH_3), 2·20 (t, 2 H, CH_2N),

1·92 (def. t, 2 H, CH_2 of the side chain adjacent to the tricycle), 1·20 (m, 2 H, CH_2 in the middle of the propane chain). For $C_{19}H_{22}ClNO_2S$ (363·9) calculated: 62·71% C, 6·09% H, 9·74% Cl, 3·85% N, 8·81% S; found: 62·84% C, 6·29% H, 9·86% Cl, 3·72% N, 8·98% S.

2-Chloro-4-methoxy-9-(3-dimethylaminopropyl)thioxanthene-9-ol (*Xb*)

The reaction of 11·0 g *VIIIb* with 3-dimethylaminopropylmagnesium chloride (from 12·0 g 3-dimethylaminopropyl chloride and 2·4 g Mg) in 100 ml tetrahydrofuran was carried out similarly like in the preceding case. The mixture was refluxed for 1 h, allowed to stand overnight and tetrahydrofuran was completely evaporated *in vacuo*. The residue was dissolved in 100 ml benzene, the solution decomposed with 50 ml 15% NH_4Cl and separated. The organic layer was shaken with 225 ml dilute hydrochloric acid (containing 25 ml concentrated acid) and the benzene layer was separated. The aqueous layer and the oily hydrochloride were made alkaline with NH_4OH and the separated base was filtered and dried; 12·8 g (88%), m.p. 141—145°C. Analytical sample, m.p. 146°C (ethanol) (Mettler). IR spectrum (Nujol): 752, 769, 833, 858, 895 (4 adjacent and solitary Ar—H), 1 069 (OH), 1 260, 1 275 ($ArOCH_3$), 1 565, 1 575 (Ar), 2 600 cm^{-1} (OH···N). For $C_{19}H_{22}ClNO_2S$ (363·9) calculated: 62·71% C, 6·09% H, 9·74% Cl, 3·85% N, 8·81% S; found: 62·90% C, 6·25% H, 9·69% Cl, 3·79% N, 9·00% S.

2-Chloro-6-methoxy-9-(3-dimethylaminopropyl)thioxanthene-9-ol (*Xc*)

A) Prepared similarly like in the preceding case from 16·6 g *VIIIc*, 18·0 g 3-dimethylaminopropyl chloride and 3·5 g Mg in 150 ml tetrahydrofuran; 19·9 g (90%), m.p. 143—148°C. Analytical sample, m.p. 153—154°C (ethanol) (Mettler). IR spectrum (Nujol): 813, 870, 893 (2 adjacent and solitary Ar—H), 1 057 (tert-OH), 1 243, 1 275, 1 306 ($ArOCH_3$), 1 486, 1 573, 1 599 (Ar), 2 650 cm^{-1} (OH···N). ^{1}H-NMR spectrum: δ 8·50 (bs, 1 H, OH), 7·90 (mcs, J = 2·0 Hz, 1 H, 1-H), 7·78 (mcd, J = 8·0; 1·0 Hz, 1 H, 8-H), 7·30 (d, J = 8·0 Hz, 1 H, 4-H), 7·13 (mcd, J = 8·0; 2·0 Hz, 1 H, 3-H), 6·90 (mcs, J = 3·0 Hz, 1 H, 5-H), 6·86 (mcd, J = 8·0; 3·0 Hz, 1 H, 7-H), 3·75 (s, 3 H, OCH_3), 2·30 (s, 6 H, CH_3NCH_3), 2·24 (t, J = 5·5 Hz, 2 H, CH_2N), 1·90 (1—4 ct, J = 5·5; 1·0 Hz, 2 H, CH_2 adjacent to the tricycle), 1·20 (m, 2 H, CH_2 in the middle of the propane chain). For $C_{19}H_{22}ClNO_2S$ (363·9) calculated: 62·71% C, 6·09% H, 9·74% Cl, 3·85% N, 8·81% S; found: 62·73% C, 5·97% H, 9·66% Cl, 3·55% N, 8·89% S.

B) A solution of 2·01 g *IIIc* in 8 ml chloroform was stirred and treated dropwise over 15 min with a solution of 3·0 g BBr_3 in 3 ml chloroform. The mixture was stirred for 6·5 h at room temperature, allowed to stand overnight, decomposed with 30 ml ethanol, stirred for 8 h, 2 ml 20% NaOH were added and the mixture was refluxed for 2 h. Ethanol was evaporated, the residue dissolved in water, the solution acidified with acetic acid and neutralized with 5% $NaHCO_3$. The precipitated product was crystallized from aqueous ethanol; 0·87 g (41%), m.p. 151—156°C. Analytical sample, m.p. 154·5—156·5°C (Kofler). For $C_{19}H_{22}ClNO_2S$ (363·9) calculated: 62·71% C, 6·09% H, 9·74% Cl, 3·85% N, 8·81% S; found: 62·90% C, 6·06% H, 9·86% Cl, 3·74% N, 8·85% S.

2-Chloro-7-methoxy-9-(3-dimethylaminopropyl)thioxanthene-9-ol (*Xd*)

The reaction of 16·0 g *VIIId* with the Grignard reagent (from 22 g 3-dimethylaminopropyl chloride and 4·3 g Mg) in 110 ml tetrahydrofuran was carried out similarly like in the preceding experiments. The mixture was decomposed with 150 ml 20% NH_4Cl solution and extracted with benzene; 20·2 g (91%), m.p. 167—172°C. Analytical sample, m.p. 172—175°C (ethanol) (Kofler). IR spectrum: 803, 819, 827, 861 (2 adjacent and solitary Ar—H), 1013, 1088, 1163 (tert-OH),

1225, 1266 ($ArOCH_3$), 1575, 1590 (Ar), 2559 cm^{-1} (OH···N). For $C_{19}H_{22}ClNO_2S$ (363·9) calculated: 62·71% C, 6·09% H, 3·85% N; found: 62·66% C, 6·00% H, 3·55% N.

2-Chloro-3-methoxy-9-(3-dimethylaminopropylidene)thioxanthene (*IIIa*)

A mixture of 9·06 g *Xa*, 60 ml water and 6·4 ml H_2SO_4 was refluxed for 1·5 h. After cooling, the solution was made alkaline with 50 ml 20% NaOH and the crude base *IIIa* isolated by extraction with benzene; 8·4 g (98%) oily mixture of geometric isomers. It was dissolved in 25 ml ethanol and neutralized with 2·42 g H_2SO_4. Crystallization gave 9·6 g hydrogen sulfate, m.p. 192—197°C. Analytical sample, m.p. 199—201°C (ethanol) (Mettler). IR spectrum: 745, 767, 867, 883 (4 adjacent and solitary Ar-H), 1226, 1264 ($ArOCH_3$), 1487, 1597 (Ar), 2520, 2770 cm^{-1} (NH^+). For $C_{19}H_{22}ClNO_5S_2$ (444·0) calculated: 51·40% C, 5·00% H, 7·99% Cl, 3·15% N, 14·44% S; found: 51·23% C, 5·29% H, 7·88% Cl, 3·14% N, 14·33% S.

2-Chloro-4-methoxy-9-(3-dimethylaminopropylidene)thioxanthene (*IIIb*)

Amino alcohol *Xb* (9·1 g) was dehydrated by boiling with dilute H_2SO_4 (18 g H_2SO_4, 70 ml water); 8·6 g (99%) glassy mixture of geometric isomers. Hydrogen sulfate, m.p. 188—190°C (ethanol) (Mettler). IR spectrum: 754, 773, 883 (4 adjacent and solitary Ar—H), 1050, 1230 ($ArOCH_3$), 1470, 1570 (Ar), 2480, 2690 cm^{-1} (NH^+). For $C_{19}H_{22}ClNO_5S_2$ (444·0) calculated: 51·40% C, 5·00% H, 7·99% Cl, 3·15% N, 14·44% S; found: 51·49% C, 5·09% H, 8·04% Cl, 3·12% N, 14·49% S.

2-Chloro-6-methoxy-9-(3-dimethylaminopropylidene)thioxanthene (*IIIc*)

Aminoalcohol *Xc* (10·0 g) was refluxed with dilute H_2SO_4 (100 ml water, 20 ml H_2SO_4) for 1·5 h and processed like in the preceding cases. The crude product obtained (9·5 g) crystallized from light petroleum; 3·45 g (36%), m.p. 68—72°C. Analytical sample, m.p. 76—79°C (Kofler). UV spectrum: λ_{max} 238·5 nm (log ε 4·63), 273 nm (4·20), 322 nm (3·46). IR spectrum (KBr) indicates the *E*-configuration: 779, 810, 847, 880 (2 adjacent and solitary Ar—H), 1231, 1245, 1266, 1289, 1299 ($ArOCH_3$), 1477, 1548, 1596 (Ar); in CS_2: 809, 821, 840, 861, 881 cm^{-1}. ^{1}H-NMR spectrum: δ 7·45 (mcs, J = 2·0 Hz, 1 H, 1-H), 7·30 (d, J = 8·0 Hz, 1 H, 4-H), 7·25 (d, J = 8·0 Hz, 1 H, 8-H), 7·10 (mcd, J = 8·0; 2·0 Hz, 1 H, 3-H), 6·92 (mcs, J = 3·0 Hz, 1 H, 5-H), 6·80 (mcd, J = 8·0; 3·0 Hz, 1 H, 7-H), 5·83 (t, J = 4·5 Hz, 1 H, C=CH), 3·80 (s, 3 H, OCH_3), 2·50 (m, 4 H, CH_2CH_2 in the chain), 2·18 (s, 6 H, CH_3NCH_3). For $C_{19}H_{20}ClNOS$ (345·9) calculated: 65·98% C, 5·83% H, 10·25% Cl, 4·05% N, 9·27% S; found: 65·57% C, 5·88% H, 10·23% Cl, 3·94% N, 9·29% S.

Hydrogen sulfate hemihydrate, m.p. 181—183°C (ethanol). For $C_{19}H_{22}ClNO_5S_2 + 0{\cdot}5\ H_2O$ (453·0) calculated: 50·38% C, 5·11% H, 7·83% Cl, 3·09% N, 14·16% S; found: 50·68% C, 5·14% H, 8·23% Cl, 3·18% N, 14·06% S.

2-Chloro-7-methoxy-9-(3-dimethylaminopropylidene)thioxanthene (*IIId*)

Aminoalcohol *Xd* (19·7 g) was dehydrated by refluxing for 2 h with a solution of 20·5 ml H_2SO_4 in 200 ml water. Processing gave 17·1 g (19%) oily mixture of geometric isomers *IIId*.

Hydrochloride monohydrate, m.p. 145—152°C (2-propanol–ether). For $C_{19}H_{21}Cl_2NOS + H_2O$ (400·4) calculated: 56·99% C, 5·80% H, 17·71% Cl, 3·50% N, 8·01% S; found: 56·80% C, 5·64% H, 17·92% Cl, 3·67% N, 7·85% S.

Hydrogen maleate, m.p. 130—135°C (2-propanol–ether). For $C_{23}H_{24}ClNO_5S$ (462·0) calculated: 59·79% C, 5·24% H, 7·68% Cl, 3·03% N, 6·94% S; found: 59·44% C, 5·38% H, 7·66% Cl, 3·06% N, 6·94% S.

Hydrogen oxalate, m.p. 82—86°C (ethanol–ether). For $C_{21}H_{22}ClNO_5S$ (435·9) calculated: 57·86% C, 5·09% H, 8·13% Cl, 3·21% N, 7·36% S; found: 57·89% C, 5·34% H, 7·81% Cl, 3·06% N, 7·21% S.

Treatment of the hydrochloride with 20% NaOH and extraction with ether gave the purified oily base which was used for recording the spectra. UV spectrum: λ_{max} 226 nm (log ε 4·53), 268 nm (4·11), infl. 286 nm (3·92), 337·5 nm (3·53). IR spectrum: 809, 839, 872, 884 (2 adjacent and solitary Ar—H), 1 227, 1 262, 1 290 ($ArOCH_3$), 1 560, 1 573, 1 591 (Ar), 2 740, 2 785, 2 825 cm^{-1} (N—CH_3). ^{1}H-NMR spectrum: δ 6·65—7·50 (m, 6 H, Ar—H), 5·90 (m, 1 H, C=CH), 3·81 and 3·80 (2 s, 3 H, OCH_3), 2·50 (m, 4 H, CH_2CH_2), 2·21 (s, 6 H, CH_3NCH_3).

2-Chloro-3-hydroxy-9-(3-dimethylaminopropylidene)thioxanthene (*IIa*)

A mixture of 210 g pyridine hydrochloride and 16·0 g *Xa* was heated for 1 h to 190°C, after partial cooling it was diluted with water, the solution filtered, the filtrate treated with a solution of 80 g NaOH in 150 ml water and extracted with benzene. The extract was dried with $MgSO_4$, evaporated and the residue was crystallized from aqueous acetone; 9·7 g (61%) solvate of base *IIa* with 0·5 CH_3COCH_3, m.p. 98—103°C (Kofler). UV spectrum (ether): λ_{max} 237 nm (log ε 4·49), 274 nm (4·11), infl. 290 nm (3·90), 323 nm (3·51). IR spectrum (CS_2): 719, 740, 758, 779 (4 adjacent Ar—H, the satellite band at 779 cm^{-1} indicates the *E*-configuration), 847, 882 (solitary Ar—H), 1 085, 1 172, 1 296 (ArOH), 1 704 (acetone), 2 565 (NH^+), 3 060 (Ar), 3 200 and 3 530 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 9·80 (bs, 1 H, OH), 7·00—7·50 (m, 5 H, Ar—H), 6·50 and 6·28 (2 s, 1 H, 4-H), 5·99 and 5·70 (2 t, 1 H, C=CH), 2·62 (bs, 4 H, CH_2CH_2), 2·18 (s, 6 H, CH_3NCH_3). For $C_{18}H_{18}ClNOS + 0{\cdot}5\ CH_3COCH_3$ (360·9) calculated: 64·89% C, 5·87% H, 9·82% Cl, 3·88% N, 8·88% S; found: 65·47% C, 6·17% H, 9·53% Cl, 3·84% N, 8·90% S.

Hydrogen maleate, m.p. 182—190°C (acetone–ether). For $C_{22}H_{22}ClNO_5S$ (447·9) calculated: 58·99% C, 4·95% H, 7·91% Cl, 3·13% N, 7·16% S; found: 59·04% C, 5·25% H, 7·93% Cl, 3·19% N, 7·24% S.

2-Chloro-4-hydroxy-9-(3-dimethylaminopropylidene)thioxanthene (*IIb*)

A) A solution of 3·45 g *IIIb* in 30 ml dichloromethane was added dropwise over 30 min to a stirred solution of 6·25 g BBr_3 in 30 ml dichloromethane under cooling with ice. The mixture was allowed to stand for 2 days at room temperature, decomposed with 60 ml water, stirred for 1 h, made alkaline with 10% Na_2CO_3 and extracted with dichloromethane. The extract was evaporated and the residue dissolved in 70 ml 3% NaOH. The solution was heated for 1 h to 100°C, filtered and the filtrate neutralized dropwise with acetic acid. After standing overnight the precipitated solid was filtered, washed with water, dissolved in 70 ml boiling ethanol, filtered again and the filtrate evaporated *in vacuo*; 2·30 g (66%) monohydrate of base *IIb*, m.p. 120—125°C. IR spectrum: 840, 905 (2 adjacent and solitary Ar—H), 1 260 (ArOH), 2 600 (OH), 2 785 and 2 880 cm^{-1} (N—CH_3). ^{1}H-NMR spectrum: δ 10·05 (bs, disappears after D_2O, 1 H, OH), 7·00—7·50 (m, 4 H, 5,6,7,8-H_4), 6·50—7·00 (m, 2 H, 1,3-H_2), 5·75 (def. t, 1 H, C=CH), 2·70 (bs, 4 H, CH_2CH_2), 2·40 and 2·30 (2 s, 6 H, CH_3NCH_3). For $C_{18}H_{18}ClNOS + H_2O$ (349·9) calculated: 61·78% C, 5·76% H, 4·00% N, 9·16% S; found: 61·56% C, 5·47% H, 3·37% N, 8·60% S.

B) A mixture of 170 g pyridine hydrochloride and 15 g *Xb* was heated for 1 h to 190°C, the melt was dissolved in 400 ml water, the solution filtered, treated with 55 g NaOH in 100 ml water

and extracted with benzene. The extract was shaken with an excess of dilute hydrochloric acid, the oily hydrochloride was isolated by decantation, decomposed with 5% $NaHCO_3$ and the product extracted with dichloromethane. The extract was evaporated, the residue dissolved in benzene and the solution treated with light petroleum; 4·0 g (29%) *E*-base *IIb* crystallized, m.p. 183—189°C. (Kofler). Analytical sample, m.p. 187—190°C (benzene–ethanol). UV spectrum (ether): λ_{max} 272 nm (log ε 4·16), 327·5 nm (3·69). IR spectrum (CS_2): 744, 758, 767, 827, 849, 898 (4 adjacent and solitary Ar—H), 1 107, 1 270 (ArOH), 2 620 (NH^+), 3 060 (Ar), 3 495 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 9·00 (bs, 1 H, OH), 7·10—7·50 (m, 4 H, 5,6,7,8-H_4), 6·95 (mcs, J = = 2·0 Hz, 1 H, 1-H), 6·78 (mcs, J = 2·0 Hz, 1 H, 3-H), 5·85 (t, 1 H, C=CH), 2·40 (s, 4 H, CH_2CH_2), 2·10 (s, 6 H, CH_3NCH_3). For $C_{18}H_{18}ClNOS$ (331·9) calculated: 65·15% C, 5·46% H, 10·68% Cl, 4·22% N, 9·66% S; found: 65·04% C, 5·40% H, 10·91% Cl, 4·15% N, 9·56% S.

Hydrogen maleate, m.p. 192—195°C (acetone–ether) (Kofler). For $C_{22}H_{22}ClNO_5S$ (447·9) calculated: 58·99% C, 4·95% H, 7·91% Cl, 3·13% N, 7·16% S; found: 58·75% C, 5·27% H, 7·80% Cl, 3·11% N, 7·12% S.

The benzene–light petroleum mother liquor gave on standing 1·2 g (9%) *Z*-base *IIb*, m.p. 173—179°C. Analytical sample, m.p. 182—184°C (benzene) (Kofler). In mixture with *E-IIb* it melts with clear depression of the melting point (160—175°C). UV spectrum (ether): λ_{max} 272 nm (log ε 4·16), 330 nm (3·69). IR spectrum (CS_2): 758, 771, 829, 855, 874, 917 (4 adjacent and solitary Ar—H), 1 107, 1 268 (ArOH), 2 560 (NH^+), 3 060 (Ar), 3 490 cm^{-1} (OH), ^{1}H-NMR spectrum (CD_3SOCD_3): δ 9·40 (bs, 1 H, OH), 7·10—7·50 (m, 4 H, 5,6,7,8-H_4), 6·90 (mcs, J = 2·0 Hz, 1 H, 1-H), 6·80 (mcs, J = 2·0 Hz, 1 H, 3-H), 5·81 (t, 1 H, C=CH), 2·38 (s, 4 H, CH_2CH_2), 2·10 (s, 6 H, CH_3NCH_3). For $C_{18}H_{18}ClNOS$ (331·9) calculated: 65·15% C, 5·46% H, 10·68% Cl, 4·22% N, 9·66% S; found: 65·21% C, 5·55% H, 10·70% Cl, 4·22% N, 9·57% S.

Hydrogen maleate, m.p. 190—192°C (acetone–ether) (Kofler). For $C_{22}H_{22}ClNO_5S$ (447·9) calculated: 58·99% C, 4·95% H, 7·91% Cl, 3·13% N, 7·16% S; found: 59·47% C, 5·13% H, 8·34% Cl, 3·30% N, 7·06% S.

2-Chloro-6-hydroxy-9-(3-dimethylaminopropylidene)thioxanthene (*IIc*)

A) A solution of 3·45 g *IIIc* in 30 ml dichloromethane was added dropwise over 45 min to a stirred and cooled solution of 7·5 g BBr_3 in 30 ml dichloromethane. The mixture was stirred for 6 h at room temperature, after standing overnight it was decomposed under cooling with 60 ml water, stirred for 1 h and made slightly alkaline with 10% Na_2CO_3. After separation, the organic layer was evaporated and the residue was heated with 70 ml 3% NaOH for 1 h to 100°C. After cooling the solid was filtered off and the filtrate was neutralized with acetic acid. The precipitated solid was filtered, heated with 100 ml boiling ethanol, filtered and the filtrate evaporated; 1·2 g (34%) monohydrate of *Z*-base *IIc*, m.p. 98—105°C. UV spectrum: λ_{max} 238 nm (log ε 4·54), 274 nm (4·19), infl. 332 nm (3·62). IR spectrum (KBr): 809. 896 (2 adjacent and solitary Ar-H), 1 098, 1 240, 1 282 (ArOH), 1 550, 1 600 (Ar), 2 580 (NH^+), 3 260 cm^{-1} (OH, H_2O); in CS_2: 809, 838, 859, 880, 891, 905 cm^{-1} (2 adjacent and solitary Ar—H). For $C_{18}H_{18}ClNOS$ + + H_2O (349·9) calculated: 61·78% C, 5·76% H, 10·13% Cl, 4·00% N, 9·16% S; found: 61·58% C, 5·50% H, 10·59% Cl, 4·11% N, 8·82% S.

B) A mixture of 16 g pyridine hydrochloride and 1·60 g *IIIc* was heated for 1·5 h to 200°C, the melt was dissolved in 100 ml water, the filtered solution neutralized with 20% Na_2CO_3 and the product extracted with dichloromethane. The extract was evaporated and the residue induced to crystallize by mixing with benzene; 0·40 g (26%) *Z*-base *IIc*, m.p. 194—197°C. Analytical sample, m.p. 200—202°C (benzene) (Kofler). UV spectrum: λ_{max} 239 nm (log ε 4·57), 275 nm (4·20), infl. 330 nm (3·58). IR spectrum (KBr): 809. 830, 846, 860, 889, 910 (2 adjacent

and solitary Ar—H), 1050, 1100, 1288 (ArOH), 1456, 1469, 1550, 1571, 1606 (Ar), 2570, 2660 (NH^+); in CS_2: 809, 840, 860, 883, 908 (Ar-H). For $C_{18}H_{18}ClNOS$ (331·9) calculated: 65·15% C, 5·46% H, 10·68% Cl, 4·22% N, 9·66% S; found: 64·88% C, 5·33% H, 10·73% Cl, 4·14% N, 9·75% S.

Hydrochloride solvated with 0·5 C_6H_6, m.p. 217—218°C (benzene–ethanol) (Kofler). For $C_{18}H_{19}Cl_2NOS + 0{\cdot}5\ C_6H_6$ (407·4) calculated: 61·91% C, 5·44% H, 17·41% Cl, 3·44% N, 7·87% S; found: 61·99% C, 5·66% H, 17·46% Cl, 3·36% N, 8·18% S.

Hydrogen maleate, m.p. 188—190°C (acetone–ethanol–ether) (Kofler). For $C_{22}H_{22}ClNO_5S$ (447·9) calculated: 58·99% C, 4·95% H, 7·91% Cl, 3·13% N, 7·16% S; found: 59·01% C, 5·19% H, 7·96% Cl, 2·91% N, 7·36% S.

C) A solution of 5·0 g *Xc* in 30 ml acetic acid was saturated for 10 min with anhydrous HBr, the mixture was refluxed for 3 h under continued saturation with HBr, allowed to stand overnight, refluxed for 3 h, diluted with 70 ml acetic acid and cooled. The precipitated red crystals (4·2 g) were filtered, dissolved in water and the solution neutralized with 20% Na_2CO_3. The precipitated product was filtered and crystallized from benzene; 0·58 g (13%) *Z*-base *IIc*, m.p. 196—199°C. Analytical sample, m.p. 200—202°C (benzene) (Kofler); the product is identical with that prepared under *B*.

2-Chloro-7-hydroxy-9-(3-dimethylaminopropylidene)thioxanthene (*IId*)

A) A mixture of 100 g pyridine hydrochloride and 10·0 g *Xd* was heated for 1 h to 190°C, the melt was dissolved in 300 ml water, the filtered solution was made alkaline with 20% Na_2CO_3 and the product extracted with benzene. The extract was dried ($MgSO_4$) and evaporated and the residue was crystallized from benzene; 2·6 g (29%) *E*-base *IId*, m.p. 190—200°C. Analytical sample, m.p. 216—217°C (benzene–ethanol) (Kofler). UV spectrum: λ_{max} 268 nm (log ε 4·12), 286 nm (3·93), infl. 340 nm (3·58). IR spectrum (Nujol): 1152, 1260, 1280, 1302, 1377 (ArOH), 1570, 1592, 1610 (Ar); in CS_2: 810, 850, 876, 892 (2 adjacent and solitary Ar-H), 2560, 2655 (NH^+), 3055, 3080 (Ar), 3300 cm^{-1} (Ar—OH···N). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 7·38 (mcs, J = 2·0 Hz, 1 H, 1-H), *c.* 7·20 (m, 3 H, 3,4,5-H_3), 6·85 (mcs, J = 3·0 Hz, 1 H, 8-H), 6·65 (mcd, J = 8·0; 3·0 Hz, 1 H, 6-H), 5·84 (bt, 1 H, C=CH), 2·40 (bs, 1 H, CH_2CH_2), 2·08 (s, 6 H, CH_3NCH_3). For $C_{18}H_{18}ClNOS$ (331·9) calculated: 65·15% C, 5·46% H, 10·68% Cl, 4·22% N, 9·66% S; found: 65·01% C, 5·68% H, 10·82% Cl, 4·05% N, 9·48% S.

Hydrogen maleate, m.p. 141—144°C (acetone–ether) (Kofler). For $C_{22}H_{22}ClNO_5S$ (447·9) calculated: 58·99% C, 4·95% H, 7·91% Cl, 3·13% N, 7·16% S; found: 59·22% C, 5·07% H, 8·00% Cl, 3·16% N, 7·29% S.

B) A solution of 10·0 g *Xd* in 150 ml acetic acid was saturated with anhydrous HCl and refluxed for 2 h. Acetic acid was evaporated, the residue was made alkaline with 20% Na_2CO_3 and extracted with benzene. The extract was evaporated and the residue heated with 70 g pyridine hydrochloride to 190°C for 1 h. The melt was dissolved in 400 ml water, the solution made alkaline with 20% Na_2CO_3 and the product extracted with benzene. The extract was dried, evaporated and the residue was crystallized from benzene; 1·67 g (18%) *E*-base *IId*, m.p. 192—200°C. Analytical sample, m.p. 216—217°C (benzene–ethanol) (Kofler); the product is identical with that prepared under *A*.

9-Bromo-2-chloro-9-(1-hydroxy-3-dimethylaminopropyl)thioxanthene (*XIII*)

A solution of 10·0 g *Z-I*-HCl (ref.[4]) in 50 ml acetic acid and 50 ml water was treated with 5 ml hydrochloric acid and a solution of 10 g KBr in 20 ml water. The stirred mixture was then treated

over 15 min with a solution of 1·58 g $KBrO_3$ in 50 ml water, added dropwise at room temperature. The solution was stirred for 30 min under cooling with ice, made alkaline with NH_4OH, the precipitated solid filtered, washed with water and dried *in vacuo*; 11·7 g (100%), m.p. 70 to 115°C. Analytical sample, m.p. 107°C with decomposition (ether) (Kofler). IR spectrum (Nujol): 751, 822, 890 (4 and 2 adjacent and solitary Ar—H), 1095 (CHOH), 1497, 1510, 1559, 1573, 1592, 3075 (Ar), 2650 cm^{-1} (N···HO). For $C_{18}H_{19}BrClNOS$ (412·8) calculated: 52·37% C, 4·64% H, 19·36% Br, 8·59% Cl, 3·39% N, 7·77% S; found: 52·38% C, 4·62% H, 18·64% Br, 8·27% Cl, 3·18% N, 8·36% S.

1-(2-Chlorothioxanthen-9-yl)-3-dimethylaminopropane-1-one (*XV*)

Crude *XIII* (16·5 g) was heated for 2 h to 130°C, the cooled melt was stirred with a small amount of acetone and filtered; 6·0 g (36%) hydrobromide of *XV*, m.p. 191—193°C. Analytical sample, m.p. 192—194°C (ethanol–acetone–ether). For $C_{18}H_{19}BrClNOS$ (412·8) calculated: 52·37% C, 4·64% H, 19·36% Br, 8·59% Cl, 3·39% N, 7·77% S; found: 52·69% C, 4·72% H, 19·22% Br, 8·22% Cl, 3·84% N, 8·00% S.

Crystallization from a mixture of 95% ethanol, acetone and ether gave the hydrobromide monohydrate, m.p. 187—189°C. IR spectrum (Nujol): 732, 742, 751, 810, 816 (Ar—H), 1561, 1576, 1593 (Ar), 1716 (aliphatic CO), 2480, 2520, 2605, 2650 cm^{-1} (NH^+). For $C_{18}H_{19}Br.ClNOS + H_2O$ (430·8) calculated: 50·18% C, 4·91% H, 3·25% N, 7·44% S; found: 49·73% C, 4·56% H, 3·04% N, 7·21% S.

Treatment of the hydobromide with NH_4OH and extraction with ether gave the oily base *XV*. ^{1}H-NMR spectrum: δ 7·10—7·40 (m, 7 H, Ar—H), 4·83 (s, 1 H, Ar_2CH), 2·45 (m, 4 H, CH_2CH_2), 2·10 (s, 6 H, CH_3NCH_3).

The mother liquor after the hydrobromide of *XV* was evaporated, the residue was made alkaline with NH_4OH and extracted with benzene. The extract was evaporated and the residue (10 g) chromatographed on a column of 500 g Al_2O_3. Elution with benzene gave 30 mg substance melting at 155—156°C (cyclohexane), identified as 2-chlorothioxanthone (*IX*). For $C_{13}H_7ClOS$ (246·7) calculated: 63·29% C, 2·86% H, 14·37% Cl; found: 63·69% C, 3·19% H, 14·47% Cl. The literature[4] reported the m.p. 147—153°C.

The chromatography was continued with a mixture of benzene and chloroform as the eluent and gave successively three products: *a*) 0·26 g substance melting at 93—99°C, identified as the starting base *Z-I*. The literature[4] reported the m.p. 98—99°C for pure compound. *b*) Small quantity of an oily base giving by treatment with HBr in ether a hydrobromide, m.p. 185—187°C (acetone–ethanol–ether), identical with *XV* hydrobromide. *c*) 0·66 g oily base giving by treatment with HCl in ether a salt, identified as 9-amino-2-chloro-9-(1-hydroxy-3-dimethylaminopropyl)-thioxanthene (*XIV*) dihydrochloride, m.p. 195—198°C (acetone–ethanol) (Kofler). Mass spectrum, *m/e* (%): M^+ is missing; 246·0142 (26) corresponding to $C_{13}H_9ClNS$ (*XVI*); 102·0912 (100) corresponding to $C_5H_{12}NO$; 58 (100) corresponding to C_3H_8N; 36 (20). IR spectrum: 737, 758, 831 (Ar—H), 1060, 1110 (CHOH), 1473, 1519, 1531, 1581, 1598 (Ar), 1619 (NH_2), 2495, 2615, 3020 cm^{-1} (NH^+, NH_3^+). For $C_{18}H_{23}Cl_3N_2OS$ (421·8) calculated: 51·25% C, 5·50% H, 25·21% Cl, 6·64% N, 7·60% S; found: 51·38% C, 5·49% H, 24·98% Cl, 6·70% N, 7·67% S.

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